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Patent

What is claimed is:

1. A method of increasing expression of a molecular chaperon by an eukaryotic cell comprising:

treating an eukaryotic cell of a living mammalian organism that is exposed to a physiological stress accompanying allergic diseases, immune diseases, autoimmune diseases, diseases of viral or bacterial origin, tumorous, skin and/or mucous diseases, epithelial disease of renal tubulus, atherosclerosis, coronarial disease, pulmonary hypertonia, cerebrovascular ischemia, stroke, or traumatic head injury with an effective amount of a chemical compound to increase the expression of the molecular chaperon by the cell beyond the amount induced by the physiological stress, wherein the chemical compound is one or more of a hydroxylamine derivative represented by formula (II),

or a salt thereof or any optically active streoisomer thereof, wherein

A is an alkyl, substituted alkyl, aralkyl, aralkyl substituted in the aryl and/or alkyl moiety, aryl, substituted aryl, heteroaryl or substituted heteroaryl group,

Z is a covalent bond, oxygen or =NR³, wherein R³ is selected from the group consisting of hydrogen, an alkyl, substituted alkyl, aryl, substituted aryl, aralkyl and aralkyl substituted in the aryl and/or alkyl moiety,

R is alkyl or substituted alkyl, and

X is oxygen, imino or substituted imino group and R' is hydrogen, an alkyl, substituted alkyl, aryl, substituted aryl, aralkyl, aralkyl having substituted aryl or alkyl moiety, acyl or substituted acyl group.

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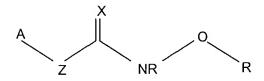
- 2. The method according to claim 1 wherein the cell is treated before the physiological stress.
- 3. The method according to claim 1 wherein the cell is treated after the physiological stress.
- 4. The method of claim 1, wherein the mammalian cell is a human cell.
- 5. The method of claim 1 wherein the cell is a neuronal cell, muscle cell, vessel wall cell, epithelial cell or a cell of the immune system.
- 6. The method of claim 1 wherein the physiological stress is metabolic, oxidative or local mechanical stress or a stress caused by hypoxia, heat shock, radiation or toxic materials.
- 7. The method of claim 1 wherein the physiological stress causes an increase of reactive free radicals or a cytokine present in the area surrounding the cell.
- 8. The method of claim 1 wherein one or more of the skin or mucosal disease is caused by dermatosis or ulcerous disease of the gastrointestinal system provoked by physiological stress.
- 9. The method of claim 1 wherein the molecular chaperon is a heat shock protein (hsp).
- 10. The method of claim 9 wherein the hsp is hsp70 or hsp72.
- 11. A method of increasing activity of a molecular chaperon in an eukaryotic cell that is exposed to a physiological stress comprising:

treating the cell that is exposed to a physiological stress accompanying allergic diseases, immune diseases, autoimmune diseases, diseases of viral or bacterial origin, tumorous, skin and/or mucous diseases, epithelial disease of renal tubulus, atherosclerosis, coronarial disease, pulmonary hypertonia, cerebrovascular ischemia, stroke, or traumatic head injury with an effective amount of a chemical compound to increase the activity of the molecular chaperon in the cell beyond the amount induced by the physiological stress, wherein the chemical compound is one or more of a hydroxylamine derivative represented by formula (II),

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or a salt thereof or an optically active stereoisomer thereof,

wherein A is an alkyl, substituted alkyl, aralkyl substituted in the aryl and/or alkyl moiety, aryl, substituted aryl, heteroaryl or substituted heteroaryl group,

Z is a covalent bond, oxygen or $=NR^3$, wherein R^3 is selected from the group consisting of hydrogen, an alkyl, substituted alkyl, aryl, substituted aryl, aralkyl and aralkyl substituted in the aryl and/or alkyl moiety,

R is an alkyl or substituted alkyl,

X is oxygen, imino or substituted imino group,

and R' is hydrogen, an alkyl, substituted alkyl, aryl, substituted aryl, aralkyl having substituted aryl or alkyl moiety, acyl or substituted acyl group.

- 12. The method of claim 11 wherein the physiological stress is metabolic, oxidative or local mechanical stress or a stress caused by hypoxia, heat shock, radiation or toxic materials.
- 13. The method of claim 11 wherein the physiological stress causes an increase of reactive free radicals or a cytokine present in the area surrounding the cell.
- 14. The method of claim 11 wherein one or more of the skin or mucosal disease is caused by dermatosis or ulcerous disease of the gastrointestinal system provoked by physiological stress.
- 15. The method of claim 11 wherein the molecular chaperon is a heat shock protein (hsp).
- 16. The method of claim 15 wherein the hsp is hsp70 or hsp72.
- 17. A method of treating a disease connected with the function of the chaperon system or associated with the injury of the membrane of a cell or cell organellum or preventing the same which comprises:

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administering to a host that has been exposed to a physiological stress accompanying allergic diseases, immune diseases, autoimmune diseases, diseases of viral or bacterial origin, tumorous, skin and/or mucous diseases, epithelial disease of renal tubulus, atherosclerosis, coronarial disease, pulmonary hypertonia, cerebrovascular ischemia, stroke, or traumatic head injury an effective amount of a chemical compound to increase the expression of a molecular chaperon by cells of the host beyond an amount induced by the physiological stress to ameliorate the effect caused by the pathological condition in the organism, wherein the chemical compound is one or more of a hydroxylamine derivative represented by formula (II),

or a salt thereof or an optically active stereoisomer thereof, wherein

A is alkyl, substituted alkyl, aralkyl, aralkyl substituted in the aryl and/or alkyl moiety, aryl, substituted aryl, heteroaryl or substituted heteroaryl group,

Z is a covalent bond, oxygen or =NR³, wherein R³ is selected from the group consisting of hydrogen, an alkyl, substituted alkyl, aryl, substituted aryl, aralkyl and aralkyl substituted in the aryl and/or alkyl moiety,

R is an alkyl or substituted alkyl, and

X is oxygen, imino or substituted imino group and R' is hydrogen, an alkyl, substituted alkyl, aryl, substituted aryl, aralkyl, aralkyl having substituted aryl or alkyl moiety, acyl or substituted acyl group.

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- 18. The method of claim 17, wherein the pathological condition is selected from the group consisting of a neoplastic disease, an infection caused by a pathogenic microorganism, an autoimmune disease and dermatosis.
- 19. The method of claim 17 wherein the host is a human organism.
- 20. The method according to claim 17, wherein

R is alkyl or substituted alkyl, and

- a) Z is chemical bond and X is oxygen, or
- b) Z is chemical bond and X is =NR4 wherein R4 is H or unsubstituted or substituted alkyl or cycloalkyl, or
 - c) Z is oxygen and X is oxygen, or
- d) Z is oxygen and X is =NR⁴ wherein R⁴ is unsubstituted or substituted alkyl, unsubstituted or substituted aralkyl, unsubstituted or substituted aryl, or heteroaryl, or
- e) Z is =NR³, wherein R³ is H, unsubstituted or substituted alkyl, aryl or aralkyl, and X is oxygen, or
- f) Z is =NR³, wherein R³ is H, unsubstituted or substituted alkyl, aryl or aralkyl and X is =NR⁴, wherein R⁴ is H, unsubstituted or substituted alkyl or aralkyl, or cycloalkyl.
- 21. The method of claim 20 wherein R is an ω -amino-alkyl which may be substituted on the amino and/or alkyl group, and wherein the alkyl chain contains 3 to 8 carbon atoms and is straight or branched, and can be substituted with hydroxy or acyloxy.
- 22. The method of claim 20 wherein R is an ω-amino-alkyl mono- or disubstituted on the amino, wherein the disubstituted amino substituents, are independently one or two straight or branched alkyl or cycloalkyl, or the disubstituted amino substituents, together with the nitrogen atom attached thereto, form a 3 to 7-membered saturated hetero ring, which may contain additional hetero atom(s).
- 23. The method according to claim 20, wherein

Z is a chemical bond,

X is oxygen,

R' is H, unsubstituted or substituted straight or branched alkyl, unsubstituted or substituted aryl, aralkyl, or aralkyl substituted in the aryl and/or alkyl moiety, and

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A is unsubstituted or substituted aryl or aralkyl, or heteroaryl.

- 24. The method of claim 23 wherein A is
 - a) phenyl, or
 - b) phenyl substituted with one or more alkyl, haloalkyl or alkoxy,
 - c) aralkyl, or
 - d) aralkyl substituted in one or more of the aryl or alkyl moiety, or
 - e) N-containing heteroaryl, or
 - f) S-containing heteroaryl.
- 25. The method according to claim 20, wherein

Z is chemical bond,

X is =NR⁴, wherein R⁴ is H, unsubstituted or substituted straight or branched alkyl, unsubstituted or substituted aryl, aralkyl substituted in the aryl and/or alkyl moiety, or cycloalkyl,

R' is unsubstituted or substituted straight or branched alkyl, unsubstituted or substituted aryl, aralkyl or aralkyl substituted in the aryl and/or alkyl moiety, and

A is aralkyl, aralkyl substituted in the aryl and/or alkyl moiety, unsubstituted or substituted aryl or heteroaryl.

- 26. The method of claim 25 wherein A is
 - a) phenylalkyl, or
 - b) phenylalkyl substituted with one or more alkoxy in the phenyl moiety, or
 - c) phenyl, or
 - d) phenyl substituted with one or more alkyl, haloalkyl or nitro, or
 - e) naphtyl, or
 - f) N-containing heteroaryl, or
 - g) an S-containing heteroaryl.
- 27. The method according to claim 20 wherein

Z is oxygen,

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X is oxygen,

R' is H, unsubstituted or substituted straight or branched alkyl, unsubstituted or substituted aryl, aralkyl, or aralkyl substituted in the aryl and/or alkyl moiety, and

A is unsubstituted or substituted straight or branched alkyl, aralkyl, or aralkyl substituted in one or both of the aryl or alkyl moiety.

- 28. The method according to claim 20 wherein Z is oxygen and X is =NR⁴, wherein R⁴ is unsubstituted or substituted straight or branched alkyl, aralkyl, aralkyl substituted in the aryl and/or alkyl moiety, unsubstituted or substituted phenyl or unsubstituted or substituted heteroaryl, and R' is unsubstituted or substituted straight or branched alkyl, unsubstituted or substituted aryl, aralkyl, or aralkyl substituted in the aryl and/or alkyl moiety.
- 29. The method according to claim 20, wherein

Z is $=NR^3$.

R³ is H, unsubstituted or substituted straight or branched alkyl, unsubstituted or substituted aryl, aralkyl, or aralkyl substituted in the aryl and/or alkyl moiety,

X is oxygen,

R' is H, unsubstituted or substituted straight or branched alkyl, unsubstituted or substituted aryl, aralkyl, or aralkyl substituted in the aryl and/or alkyl moiety, or acyl, and

A is unsubstituted or substituted alkyl, aralkyl, aryl or heteroaryl or cycloalkyl.

- 30. The method according to claim 29 wherein A is
 - a) unsubstituted or substituted straight or branched alkyl which contains 4 to 12 carbon atoms, or
 - b) cycloalkyl, or
 - c) unsubstituted or substituted phenylalkyl, or
 - d) phenyl, or
 - e) phenyl substituted with one or more halo, alkyl, haloalkyl, alkoxy or nitro, or
 - f) an N-containing heterocyclic group.
- 31. The method according to claim 20, wherein

Z is =NR³, wherein R³ is H, unsubstituted or substituted straight or branched alkyl, unsubstituted or substituted aryl, aralkyl, or aralkyl substituted in the aryl and/or alkyl moiety,

X is =NR⁴, wherein R⁴ is H, unsubstituted or substituted straight or branched alkyl, unsubstituted or substituted aryl, aralkyl, or aralkyl substituted in the aryl and/or alkyl moiety or cycloalkyl, and

R' is unsubstituted or substituted straight or branched alkyl, unsubstituted or substituted aryl, aralkyl, or aralkyl substituted in the aryl and/or alkyl moiety, and

A is unsubstituted or substituted straight or branched alkyl or unsubstituted or substituted aryl.

32. Hydroxylamine derivatives of the formula (II)

wherein

a) X is oxygen,

A is C₁₋₂₀ straight or branched alkyl, unsubstituted or substituted aryl, unsubstituted or substituted aralkyl, naphtyl or N-containing heteroaromatic group,

Z is chemical bond,

R' is H, C¹⁻⁴ alkyl or aralkyl, and

R is a group of the formula (b),

$$--(CH2)k--CH--(CH2)m-N R5$$

$$+$$

$$+$$

$$+$$

$$+$$

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where R^5 and R^6 are independently H, straight or branched alkyl, or cycloalkyl, or R^5 and R^6 , when taken together with the N-atom adjacent thereto, form a 3 to 7-membered saturated heterocyclic ring, Y^6 is H or $-OR^7$ wherein R^7 is H, k is 1, 2 or 3, and m is 1, 2, or 3, with the proviso that when A is other than alkyl and R^7 is H, Y^6 is H, or

b) X is =NR⁴, wherein R⁴ is H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, or unsubstituted or substituted aralkyl,

A is unsubstituted or substituted aryl, or unsubstituted or substituted aralkyl, or cycloalkyl,

Z is chemical bond, oxygen or $=NR^3$, wherein R^3 is H or unsubstituted or substituted alkyl,

R is unsubstituted or substituted alkyl or unsubstituted or substituted aryl, or unsubstituted or substituted aralkyl, and

R is a group of the formula (b), wherein R⁵ and R⁶ are independently H, straight or branched alkyl, or cycloalkyl, or R⁵ and R⁶, when taken together with the N-atom adjacent thereto, form a 3 to 7-membered saturated heterocyclic ring, Y⁶ is H or -OR⁷ wherein R⁷ is H or unsubstituted or substituted alkylcarbonyl or arylcarbonyl, k is 1, 2 or 3, and m is 1, 2 or 3, or

c) X is oxygen,

A is unsubstituted or substituted alkyl, unsubstituted or substituted aralkyl,

Z is oxygen,

R' is alkyl or aralkyl,

R is a group of the formula (b), wherein R^5 and R^6 are independently H, straight or branched alkyl, or cycloalkyl, or R^5 and R^6 , when taken together with the N-atom adjacent thereto, form a 3 to 7~membered saturated heterocyclic ring, Y^6 is H or -OR⁷ wherein R^7 is H or unsubstituted or substituted alkylcarbonyl or ary1carbonyl, k is 1, 2 or 3, and m is 1, 2 or 3, or

d) X is oxygen,

Z is =NH and

A is unsubstituted or substituted alkyl, cycloalkyl, unsubstituted or substituted aralkyl, phenyl or phenyl substituted with halo, alkyl, haloalkyl, alkoxy or nitro,

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R' is alkyl or aralkyl, and

R is a group of the formula (b), wherein R^5 and R^6 are independently H, straight or branched alkyl, or cycloalkyl, or R^5 and R^6 , when taken together with the N-atom adjacent thereto, form a 3 to 7-membered saturated heterocyclic ring, Y^6 is H or -OH, k is 1, 2 or 3, and m is 1, 2 or 3.

- 33. The hydroxylamine derivatives of claim 32, wherein A is phenyl, substituted phenyl or phenylalkyl.
- 34. Pharmaceutical composition, and said composition's pharmaceutically acceptable carriers and auxiliaries, for the treatment of cardiovascular, vascular, cerebral, allergic, immune, autoimmune diseases, diseases caused by viral or bacterial infections, tumorous, skin or mucosal diseases, wherein the said composition contains 0,5 to 99,5 % by weight of a hydroxylamine compound of the formula (II)

wherein

a) X is oxygen,

A is C₁₋₂₀ straight or branched alkyl, unsubstituted or substituted aryl, unsubstituted or substituted aralkyl, naphtyl or N-containing heteroaromatic group,

Z is chemical bond,

R' is H, C1-4 alkyl or aralkyl, and

R is a group of the formula (b),

$$---(CH_2)_k$$
----CH---(CH₂)_m-N R^5

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where R^5 and R^6 are independently H, straight or branched alkyl, or cycloalkyl, or R^5 and R^6 , when taken together with the N-atom adjacent thereto, form a 3 to 7-membered saturated heterocyclic ring, Y^6 is H or $-OR^7$ wherein R^7 is H, k is 1, 2 or 3, and m is 1, 2, or 3, with the proviso that when A is other than alkyl and R^7 is H, Y^6 is H, or

b) X is =NR⁴, wherein R⁴ is H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, or unsubstituted or substituted aralkyl,

A is unsubstituted or substituted aryl, or unsubstituted or substituted aralkyl, or cycloalkyl,

Z is chemical bond, oxygen or =NR³, wherein R³ is H or unsubstituted or substituted alkyl,

R is unsubstituted or substituted alkyl or unsubstituted or substituted aryl, or unsubstituted or substituted aralkyl, and

R is a group of the formula (b), wherein R⁵ and R⁶ are independently H, straight or branched alkyl, or cycloalkyl, or R⁵ and R⁶, when taken together with the N-atom adjacent thereto, form a 3 to 7-membered saturated heterocyclic ring, Y⁶ is H or -OR⁷ wherein R⁷ is H or unsubstituted or substituted alkylcarbonyl or arylcarbonyl, k is 1, 2 or 3, and m is 1, 2 or 3, or

c) X is oxygen,

A is unsubstituted or substituted alkyl, unsubstituted or substituted aralkyl,

Z is oxygen,

R' is alkyl or aralkyl,

R is a group of the formula (b), wherein R^5 and R^6 are independently H, straight or branched alkyl, or cycloalkyl, or R^5 and R^6 , when taken together with the N-atom adjacent thereto, form a 3 to 7~membered saturated heterocyclic ring, Y^6 is H or -OR⁷ wherein R^7 is H or unsubstituted or substituted alkylcarbonyl or ary1carbonyl, k is 1, 2 or 3, and m is 1, 2 or 3, or

d) X is oxygen,

Z is =NH and

A is unsubstituted or substituted alkyl, cycloalkyl, unsubstituted or substituted aralkyl, phenyl or phenyl substituted with halo, alkyl, haloalkyl, alkoxy or nitro,

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R' is alkyl or aralkyl, and

R is a group of the formula (b), wherein R^5 and R^6 are independently H, straight or branched alkyl, or cycloalkyl, or R^5 and R^6 , when taken together with the N-atom adjacent thereto, form a 3 to 7-membered saturated heterocyclic ring, Y^6 is H or -OH, k is 1, 2 or 3, and m is 1, 2 or 3.